REMARKS/ARGUMENTS

Claims 9-13 have been cancelled herein. Claim 14 had been amended to include the subject matter of cancelled claim 9. Claim 14 has further been amended to recite "embryonic stem cells" instead of "embryonal cells". The use of embryonic stem cells in the creation of transgenic animals is explicitly described in the specification at, for example, page 63, line 17 and page 64, line 20. No new matter has been added by way of these amendments.

Rejections Under 35 USC § 112, 1st Paragraph

The Office has rejected claims 1-8 and 14 under 35 U.S.C. § 112, 1st Paragraph as not enabled by the specification. Specifically, the Office states that the specification fails to provide guidance or working examples correlating to the creation of a transgenic mouse expressing the recited transgene. However, the specification, in Example II, page 51, "Cloning the mouse α MHC gene" describes the cloning of the gene, the transformation of mouse embryonic stem (ES) cells and the microinjection of the ES cells into a blastocyst. The example further describes the mating of chimeric mice to C57Bl/6 partners and that the result is agouti pups that are analyzed by Southern blot for the presence of the knock-in chromosome. Further, in the section headed "Generation of Mice with Mutant MHC's" beginning on page 61, the specification describes the generation of transgenic mice expressing MHC's in which loop 1, the IMD or both have been mutated. Further, the section titled "Development of mutant loop 1 and IMD mouse lines" again describes the generation of a transgene-carrying ES cell, the microinjection of the clones into blastocysts, the production of chimeric mice and the resulting homozygous offspring generated by the mating of the chimeras. Thus, contrary to the Office's assertion that the generation of the claimed transgenic animal is not enabled, the

production of the claimed transgenic mouse is described such that one of skill in the art could generate the recited transgenic mouse.

Further, the applicant's point out that, though the Office asserts that the production of transgenic animals is not reliable, the production of transgenic animals is a routine venture both at most high-level academic institutions and at commercial enterprises. As an example, the University of Wisconsin - Madison (UW) provides a Transgenic Animal Facility (TAF) to serve faculty wishing to study transgenic animals (and where the transgenic strain of the instant invention was created) (see Exhibit 1, attached hereto). Further, the information page for the University of Wisconsin Transgenic Animal Facility, as of February 11, 2004, states "TAF *routinely* microinjects transgenes into the pronucleus of FVB/n and C57BL/6 1-cell embryos" emphasis added. See, http:// www.biotech.wisc.edu/ServicesResearch/TransgenicAnimal/TransgenicMice orRats.asp. In fact, a search of the internet, using Google®, for "transgenic facility" indicates that just about every major university in the United States (and most major universities around the world) have, at least, one transgenic core facility for the production of transgenic animals according to investigator needs. Commercial vendors of transgenic animals include: Charles River Laboratories (see, http://www.criver.com/ flex_content_area/documents/rm_tg_c_transgenic_services.pdf); B & K Universal Ltd (see, http://www.bku.com/labanimals.html#transgen) and GenOway (see, http://www. genoway.com/service.htm). Thus, contrary to the Offices assertion that one could not rely on the state of the art to produce the disclosed transgenic mouse, the production of such animals is a thriving venture both at academic institutions and commercial businesses. Therefore, not only is the production of transgenic animals well know in the art but, their production is generally provided for by specialized laboratories following

the instructions of a scientific investigator who merely provides a transgene vector for microinjection into oocytes, as is specifically described in the specification at, for example, pages 51-53. Thus, the specification fully describes the material necessary for the production of a transgenic animal. Therefore, this rejection has been overcome and should be withdrawn.

As a second issue, the Office rejects Claim 14 under 35 U.S.C. § 112, 1st Paragraph for the recitation of "embryonal cells." In response, claim 14 has been amended herein to recite "embryonic stem cell". The use of embryonic stem cells (and ES cells) in the generation of transgenic animals is used throughout the specification at, for example, page 63, line 17 and page 64, line 20. Therefore, this rejection has been overcome and should be withdrawn.

As a third issue, claims 6-8 are rejected under 35 U.S.C. § 112, 1st Paragraph. Specifically, the Office states that the specification fails to provide a transgenic mouse with a reduced heart rate phenotype for use in studying molecular and cellular aspects. Further, the Office states, it would have required undue experimentation to practice the invention for treating cardiac diseases by overexpression of mutant alpha MHC gene without a reasonable expectation of success because the specification has failed to provide a transgenic mouse having the physiological properties described. The applicants herein refer to the declaration of Richard L. Moss, Ph.D., Chairman of the University of Wisconsin Department of Physiology and a co-inventor on the instant invention attached hereto as Exhibit 2. As described in Dr. Moss' declaration, the transgenic mouse described in the specification has been produced and its physiological characteristics correlate to those describe in the specification. Specifically, the transgenic animal has

heart muscle displaying a slower rate of contractility, greater generation of force, greater overall force and reduced heart rate as shown in **Figures 2A** and **B** and **Tables A** and **B** in the inventor's declaration. Further, while the transgenic mouse described in the specification may be used to study various cardiovascular diseases and coronary physiology, the specification does give specific examples of uses for the transgenic mouse, at for example, pages 8-10, with specific examples of the tests used being provided in the specification at for example pages 66-71. Thus, the rejection has been overcome and should be withdrawn.

Finally, the Office states that Claims 1-5 and 14 embrace a homozygous or heterozygous transgenic mouse with a reduced heart rate. However, it is well accepted in the art that a transgenic mouse strain is by definition homozygous, (see, for example http://home.comcast.net/~john.kimball1/BiologyPages/T/TransgenicAnimals.html, copy attached hereto as Exhibit 3, and http://www.sinauer.com/milestones-devbio/Gilbert7e_100-101.pdf, attached hereto as Exhibit 4 for the examiner's convenience) if the strain is not homozygous for the desired gene, then any mating with another mouse would only have a 1:4 chance of receiving the desired transgene and therefore would not breed true and thus could not be considered a "strain". In the current instance, the offspring of the implanted female will be heterozygous and are mated to wild type animals. This mating results in a litter that is either wild type or heterozygous for the transgene. The heterozygotes are then crossed that results in a litter that is 1:4 homozygous for the transgene, following standard Mendelian genetics. Thus, in discussing the creation of a transgenic mouse, Applicants wish to point out that the definition *a priori* comprises the homozygous animal. Thus, the rejection has been overcome and should be withdrawn.

CONCLUSION

In view of the amendments and arguments presented herein, Applicants respectfully request reconsideration and a timely notice of allowance to follow in this case. Applicants request that the Examiner telephone the undersigned in the event a telephone discussion would be helpful in advancing the prosecution of the present application. The Commissioner is authorized to charge any additional fees or underpayment of fees regarding this response, including extensions for reply, to Deposit Account 07-1509.

Respectfully submitted,

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